IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, ADRIAN PAUL BROWN, M.A., M.I.L., M.I.T.I., declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.

2. That I am well acquainted with the German and English languages.

3. That the attached is a true translation into the English language of the attached German text filed at the US Patent and Trademark Office on 25th February 2002.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 16th DAY OF APRIL 2002

A. P. Brown

A. P. BROWN

Resorbable bone replacement and bone formation material

Prior art

a) Phase purity

Since the sixties, calcium orthophosphates, especially α- and β-tricalcium phosphate (TCP) and also hydroxyapatite (HAP) have been investigated and used as so-called bioactive and resorbable bone replacement materials. A comprehensive materials science and biomedical literature exists on the subject, in which respect, by way of example, reference may here be made to the comprehensive summary by K. deGroot: Bioceramics of Calciumphosphates. K.deGroot (Editor) CRC Press, Bota Raton, Fl. 1983, 1.
The good biocompatibility of that group of materials is understandable considering the extensive chemical similarity of those materials to the inorganic constituent of bone, hydroxyapatite. The scientific discoveries from the period of pioneering research into that group of materials are adequately described by the work referred to above.
Accordingly, the good compatibility with bone, the more or less pronounced resorbability and the so-called "bioactivity" are reported, bioactivity being understood to mean the positive chemical interaction of those calcium phosphates with living bone, which finds expression in the formation of a direct bond, without connective tissue, with the bone.
The precise links between the materials characteristics and the biological properties of those materials have not, as yet, been clarified in many regards and it is only in recent times that discoveries have been made in respect of the correlation between the materials science, thermodynamic and crystallographic characteristics of those materials and the biological reactions of bone.

In the case of foreign-body reactions of bone it is generally assumed that particles less than 20 micrometers in size are taken up and transported away or metabolised (phagocytosis) by macrophages (phagocytes). Those processes are discussed, *inter alia*, in the following publications: Meachim *et al.* in Biomaterials, 3 (4) (1982) 213-219 and Sioholm *et al.* in J. Pharmacol. Exp. Ther., 211 (3) (1979) 656-662.

In a further study, deGroot reports (DeGroot *et al.*: Die klinische Anwendbarkeit von Calciumphosphat Keramiken [The clinical applicability of calcium phosphate ceramics]. Z.M.Fortbildung **75**, 1985, 1938 – 1940) on the particulate breakdown of TCP into phagocytosable sub-particles which can pass into the lymphatic system. According to findings on which the invention is based, those phenomena have something to do with the phase make-up, phase purity and structure of the TCP material investigated therein. Accordingly, the two most important forms of TCP, α- and β-TCP, despite their chemical similarity, have different solubilities and, especially, different conversion characteristics in the biological environment. In many TCP materials, the two forms of tricalcium phosphate are present together, with phases of lesser stability (lattice energy and solubility) being concentrated at the particle boundaries. When heterogeneous materials of that kind are subjected to continuing chemical dissolution and biological degradation processes, such a material will break down in the manner described by De Groot. Because of the concentration of "foreign phases" at the particle boundaries of the principal constituents of the material, that breakdown process mechanism is active even when there are very small amounts of phase impurities. From that it follows that such resorbable implant materials must be very carefully synthesised in phase-pure form. In the case of materials corresponding to the prior art, that requirement is clearly not met. (G. Bauer and G. Hohnberger: Ursachen unterschiedlichen Verhaltens von bioaktiven Calcium Phosphatkeramiken im Organismus [Causes of differing behaviour of bioactive calcium phosphate ceramics in the body]. cfi (Ber. d . DKG) 66 (1989), 23-27)

b) Porosity

- Microporosity –

Microporosity is understood to mean that porosity of a ceramic material which is no longer discernible to the naked eye, that is to say pore radii that are approximately ≤ 20 micro-meters (Römpp Chemie Lexikon [Römpp Chemistry Dictionary], 7th Edition (1975), Franckh'sche Verlagshandlung, Stuttgart).

In addition to the phase purity, the nature of the pore structure of a resorbable bone replacement material is an important factor.

To begin with, it should first be stated that increasing the porosity of the structure increases the specific surface area and also, as a result, the resorbability. At the same time, the mechanical strength decreases and the tendency to particulate breakdown increases. In spite of that basic relationship, the prior art attempts to achieve a resorption rate that is as high as possible by providing the internal surface of the material with particle-to-particle binding that is as weak as possible by using or "cultivating" constituents of the structure that are as finely particulate as possible. As expected, biomaterials according to the prior art that are "cultivated" for high resorption rates are mechanically so imperfect that they generally come into consideration only for applications in which no appreciable mechanical demands are made. The uncontrollable breakdown into microscopically fine sub-particles results, moreover, in increased formation of polynuclear giant cells, which has to be regarded as an unfavourable cellular reaction to the biomaterial in question.
Rapid implant resorption occurring synchronously with restoration of newly formed bone, without the occurrence of any appreciable breakdown of the structure, is desirable.

According to the prior art, relatively large, formed, monolithic pieces made from such microporous materials are also used as implants for bridging relatively large bone defects. In the case of such formation materials, in which only microporous material structures are present, it is found that, after superficial resorption, pronounced stagnation of the resorption process takes place after a short time and, later, rejection processes may even occur. According to findings on which the invention is based, those phenomena are in no way to be attributed to the chemical material properties of the calcium phosphates in question but, rather, are based on the following negative effect: The microporosity of those materials actually has a capillary suction effect on fluids in the region surrounding the implant. As a result, those fluids are drawn into the interior of the implant materials, where they remain for relatively long periods while newly formed bone grows around the external regions of the implant. Bone structures and blood vessels are not able to penetrate into the internal regions and the diffusion distances are too large for a diffusive exchange of substances. Accordingly, in the interior of such "inaccessible" regions of monolithic implant materials, necrosis of the body fluids and cells previously drawn in by the capillary action may occur.

- Macroporosity –

According to Römpp Chemie Lexikon [Römpp Chemistry Dictionary], 7th Edition (1975), Franckh'sche Verlagshandlung, Stuttgart, macroporosity is understood to refer to pore radii $\geq$ 20 micrometers.

From as early as the seventies the possibility has been investigated of using calcium phosphate implant materials which have an open, interconnected macroporosity (K. Köster, H. Heide and R. König: Histologische Untersuchungen an der Grenzfläche zwischen Knochengewebe und Calciumphosphatkeramik etc. [Histological investigations at the boundary surface between bone tissue and calcium phosphate ceramic etc.], Z. Orthop. **115**, (1977), 693 – 699) in order to make it possible for bone to penetrate as quickly as possible.

That aspect is a feature of many products corresponding to the prior art. However, macroporous products of that kind corresponding to the prior art have serious disadvantages, which shall be discussed below:

- one of the current methods for producing a macroporous structure consists of adding porosity-imparting agents, which are introduced, for example, in the form of foams or spherical plastics, which give rise to spherical pores on solidification of a hydraulically setting starting compound or on ceramic baking.
  That porosity-imparting method has the disadvantage that the pores are predominantly closed. They are accordingly not available for penetration by budding-in bone and, in the end, result only in lowering of the strength of the implant region.

- A similar effect is produced by porosity-imparting methods carried out in many different ways by burning out irregularly shaped organic "spacer materials". In ceramics technology, sawdust, for example, is conventionally used. In that method and in numerous similar porosity-imparting media, irregularly distributed pore shapes and sizes are formed - which can be described as statistical porosity - which are used in ceramics technology for reducing the weight of the materials concerned and for improving thermal insulation. Statistical porosities of that kind are also used, based on those methods, in biomaterials according to the prior art. They are, however,

completely unsuitable for the purpose, for the following reasons: Statistical porosities contain a wide spread of pore radius distribution, as well as, especially, numerous closed pores and pore tracks having "dead ends", which are unsuitable for homogeneous and complete penetration by bone.

- Building on that finding, a further kind of pore structure, obtained from biogenic products, is also currently in use. One such pore structure is so-called spongy bone, for example from cattle bone, which for the purpose of being used as implant material, is conditioned by more or less complete removal of protein constituents. Also used are the porous structures of corals and certain algae in order to obtain pore structures which, in view of their biogenic formation, are apparently optimal. Apart from the chemically questionable properties of such substances (for example, undefined chemical compositions and immunological problems in the case of cattle bone etc., as well as chemical activities that are entirely different to that of bone in the case of the use of algae and corals), there are also reasons of principle why such pore structures cannot be considered especially suitable: To begin with, it may first be stated that although the mentioned pore structures, as end products of a cybernetic modification process, have formed optimally modified systems in the original organisms in question, those systems no longer bear any relation to the biomechanical demands in the implant site. (In such a biomaterial, bone can necessarily only form in the open pore spaces, which in the original organism were holes or, in other words, were <u>not</u> biofunctional loading zones. At best, therefore, the "negative" of a functional bone structure can be formed.) Even disregarding such relatively "philosophical" reasons, the basic arguments against "statistical porosities" also argue against such structures: In the case of such biogenic pore structures, ingrowing bone structures are also impeded, for example, as a result of pores that are too small, or the osteons budding in are prevented, by numerous changes in direction, from achieving a biofunctional, lamellar orientation as quickly as possible, actually causing the formation of "woven bone", which grows in unordered fashion.

The invention accordingly relates to a resorbable bone replacement and bone formation material (augmentation material) based on porous β-tricalcium phosphate (β-TCP).

In the case of the formation material according to the invention, the macropores, seen in themselves, can contribute approximately 35 % to the overall porosity (that is to say, microporosity + macroporosity) of the material. In spite of the high overall porosity of more than 50 %, the strength of this implant material, compared to a statistical porosity of the same order of magnitude, is still sufficiently high for formed implant pieces still to be very readily handled. Without doubt, however, the strengths are so low here that functional strengths of the implant sites cannot be achieved without additional mechanical supporting devices, such as, for example, an external fixation or the known screw arrangements with plates etc. in many cases immediately after implantation. One of the crucial advantages of the formation material according to the invention is, however, that cross-linking of the implant structure with functionally oriented and spatially cross-linked bone structures takes place very rapidly so that, compared to other implant materials corresponding to the prior art, very rapid restoration of the functional loadability of the implant zone is achieved. Consequently, the naturally low strength of calcium phosphate materials is compensated solely by the macroporous structure according to the invention. Even during the penetration phase of such structures, the osteons that bud in, which are already matched in their functional orientation to the loading situation, quickly supply the entire implant region with vessels and, consequently, ensure rapid resorption of the formation material according to the invention, with - simultaneously - a biofunctionally loadable state being very quickly achieved. The bone replacement and formation material according to the invention meets the general requirement for restoration of the implant site as quickly as possible solely by means of the described features with respect to

- phase purity
- microporosity and
- function-matched macroporosity

in ideal manner. Those positive factors can be further enhanced by combining the implant materials according to the invention with growth-promoting constituents of the patient's blood, the so-called platelet rich plasma or so-called bone morphogenic proteins. That can be accomplished, for example, by soaking the micro- and macro-porous spaces of the implant materials, immediately before the operation, with preparations, in liquid form, of the growth-promoting media.

Further aspects of the solution to the technical problems and advantages of the bone replacement and formation material according to the invention are set out hereinbelow.

The invention further relates to a formation material characterised in that the chemical and crystalline purity, the fabric structure, the microporosity and the macroporosity of the augmentation material make possible rapid, foreign-body-reaction-free, biochemically orientated integration and resorption in bone.

Furthermore, the formation material according to the invention can be characterised in that at least 99.5 % of the material consists of pure β-tricalcium phosphate (β-TCP).

Furthermore, the formation material according to the invention can be produced by baking β-tricalcium phosphate (β-TCP) at least twice and especially at least three times and preventing the formation of thermodynamically stable adjacent phases of β-TCP.

Furthermore, the formation material according to the invention can be produced by

(i) baking a phosphate powder of a chemical composition the residue on baking of which yields theoretically chemically pure tricalcium phosphate as a sintered-together presynthesis product, and powdering that presynthesis product,

(ii) optionally baking the powdered presynthesis product together with phosphate powder according to step (i) and powdering the material obtained and optionally repeating step (ii) once or more than once,

(iii) compressing the powdered product obtained in step (i) or step (ii) together with phosphate powder according to step (i) to form blanks and subjecting the blanks formed to final ceramic baking and

(iv) providing the compressed or baked blanks with tubular pores.

Furthermore, the formation material according to the invention can be produced by

(i) starting from a presynthesis product obtainable by baking a phosphate powder of a chemical composition the residue on baking of which yields theoretically chemically pure tricalcium phosphate as a sintered-together presynthesis product, and powdering that presynthesis product,

(ii) optionally baking the powdered presynthesis product together with phosphate powder according to step (i) and powdering the material obtained and optionally repeating step (ii) once or more than once,

(iii) compressing the powdered product obtained in step (i) or step (ii) together with phosphate powder according to step (i) to form blanks and subjecting the blanks formed to final ceramic baking and

(iv) providing the compressed or baked blanks with tubular pores.

Furthermore, the formation material according to the invention can be obtainable by baking at a temperature below 1200°C in the β-tricalcium phosphate (β-TCP) phase region.

Furthermore, the formation material according to the invention can be obtainable by using in step (ii) and/or step (iii) from 1 to 50 % by weight, especially from 1 to 25 % by weight, phosphate powder (based on the total weight of phosphate powder and already baked material).

Furthermore, the formation material according to the invention can be characterised in that the sintered structure has a uniform, interconnected microporosity with pore widths in the region of from 2 to 15 µm and especially from 4 to 10 µm and/or the matrix of the augmentation material is tightly sintered to microporosity, especially with microparticles that are loosely incorporated in the sintered structure and/or phagocytosable, having a diameter of max. 15 µm, being absent.

Very advantageous cellular reactions are found if the bone replacement material has the structural parameters according to the invention: As a result of the production route, which shall be discussed hereinbelow, the material according to the invention is distinguished by an open, interconnecting microporosity having pore widths of from 2 to 15 µm. The ceramic

matrix itself constitutes a network of tight structural elements firmly sintered to one another, in which loosely incorporated sub-particles, which could be dissolved out by cell activities, are absent.

Furthermore, the formation material according to the invention can be characterised by a microporosity of 20 % by volume or more, preferably from 20 to 40 % by volume, and especially 30 % by volume or more, of the overall porosity (consisting of micro- and macro-porosity).

Also characteristic of the micro-structure according to the invention are the rounded surfaces of the fabric-forming structural elements (cf. **Fig. 1**), which relate especially advantageously to the living cells in the implant site, because mechanically induced irritation of the site tissue is largely avoided as a result. Those rounded fabric elements also cause stress and strain in the materials science sense to be minimised so that the materials according to the invention have optimum mechanical strength despite their comparatively high microporosity of more than 30 % by volume.

Furthermore, the formation material according to the invention can be obtainable by providing the compressed blank with tubular pores with the aid of a compression mould of optionally more than one part.

Furthermore, the formation material according to the invention can be obtainable by providing the baked blank with tubular pores by means of milling or drilling.

Furthermore, the formation material according to the invention can be characterised in that the formation material is in block form, with 2- or 3-dimensionally oriented macroscopic tubular pores passing through each block, which are in each case arranged perpendicular to the block surface or to an imaginary plane laid through the block or against the block and form an interconnecting system of tubular pores.

Furthermore, the formation material according to the invention can be characterised in that a block intended for implantation, together with its tubular pores, can be so oriented for implantation or on processing prior to implantation that at least one direction of orientation

of the tubular pores corresponds to a biomechanically or biofunctionally intended direction of growth.

Furthermore, the formation material according to the invention can be characterised by tubular pores that have radii in the region of from 100 to 2000 µm and especially from 500 to 2000 µm.

In contrast to the prior art, the bone replacement and formation material according to the invention is provided with a very regularly oriented tubular porosity which, with radii of preferably from 500 to 2000 µm, has optimum size characteristics for the budding-in of osteons. Such pores of parallel arrangement pass through the materials according to the invention in at least two, in certain applications even three, tubular systems arranged perpendicular to one another. For optimum matching to the functional task, one of the tube orientations on implantation should be in accordance with the main direction of growth of the adjacent host bone. Because the pore systems arranged perpendicular to one another in the implant materials according to the invention interconnect in all planes, the bone structures that bud in cross-link very quickly to form a well vascularised spatial network of load-bearing bone structures. As a result, the bone formation material according to the invention constitutes, in the truest sense of the term, an optimum guide rail system.

That accords with studies by Klawitter *et al.* (Klawitter, J.J. *et al.:* An Evaluation of Bone Growth into Porous High Density PE. J.Biomed.Res.10:311, 1976), according to which the smallest functional building elements of bone, the osteons, which are tube-like structures having complete supply organs for maintaining vital functions, can only grow into pore tracks that have a pore width of at least 100 µm. Smaller pore systems do not permit biofunctional penetration by living bone. From that it follows that biomaterials having statistical pore systems, for example those corresponding to the current prior art, cannot be a satisfactory solution.

Furthermore, the formation material according to the invention can be characterised in that the formation material, present in block form, is penetrated by the tubular pores spaced apart at a defined spacing with respect to one another, especially at a spacing that corresponds to a wall thickness of not more than from 1500 to 4000 µm and especially from 2000 to 3000 µm.

According to further investigations upon which the invention is based, the critical material thicknesses in the case of monolithic material structures having solely microporosity are above 3 – 4 mm. If the wall thickness is lower, the body fluids can be exchanged with the surrounding living tissue by means of diffusive processes so that necrotic processes do not take place.

The requirement arrived at above in the section "Microporosity" for wall thicknesses of not more than from 3 to 4 mm is met in the defined macroporous material according to the invention by means of the fact that the tubular pores are set so closely together that the material thicknesses are at no point greater than about 3 mm.

Furthermore, the formation material according to the invention can be characterised by an overall porosity (consisting of micro- and macro-porosity) of more than 50 % by volume.

Furthermore, the formation material according to the invention can be characterised by a macroporosity of from 25 to 50 % by volume, and especially from 30 to 40 % by volume, of the overall porosity (consisting of micro- and macro-porosity).

Furthermore, the formation material according to the invention can be characterised in that the block form is a simple geometric shape, especially that of a cube, cuboid, taper, cone or disc.

Furthermore, the formation material according to the invention can be characterised in that it is a semi-finished product, especially for subsequent mechanical processing, preferably for individual adaptation in the case of a bone defect in mouth or jaw medicine, orthopaedic surgery or trauma surgery.

Furthermore, the formation material according to the invention can be characterised in that the material is compressed, especially baked or sintered, only to a degree such that it can be processed using tools available to the practitioner, especially using a rasp, file, scalpel or a dentist's instrument.

Furthermore, the formation material according to the invention can be characterised in that it has been brought into the form of an individual prosthesis with the aid of a medical CAD/CAM method.

The invention is illustrated in further detail hereinafter by means of figures and implementation examples, wherein:

Fig. 1 shows the micro-structure of an augmentation material according to the invention;

Figs. 2a to 2d show examples of augmentation articles according to the invention in the form of semi-finished products;

Fig. 3a shows an alveolar augmentation article according to the invention;

Fig. 3b shows an augmentation article according to the invention for a trephination closure; and

Fig. 3c shows an augmentation article according to the invention in the form of a sinus lift.